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Association of PS1 1/2, ACE I/D, and LRP C/T polymorphisms with Alzheimer's disease in the Chinese population: a meta-analysis of case-control studies

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ABSTRACT. The objective of this study was to assess the associations of presenilin 1 (PS1) 1/2, angiotensin I-converting enzyme (ACE) insertion/deletion (I/D), and low-density lipoprotein receptor-related protein (LRP) C/T polymorphisms with the risk of Alzheimer's disease (AD) in the Chinese population. PS1 1/2, ACE I/D, and LRP C/T, which are commonly investigated polymorphisms, were evaluated to obtain summary estimates regarding their associations with AD. In total, the data from 24 studies (2611 patients with AD and 2822 control subjects from 23 provinces and special districts in China) that were obtained from the Chinese Biomedicine Database, China National Knowledge Infrastructure, PubMed, and Medline were included. Different models (i.e., dominant, recessive, etc.) of these polymorphisms were analyzed using the Cochrane

Review Manager. Statistically significant associations among patients with AD for the 1/1 genotype of the PS1 1/2 polymorphism [odds ratio (OR) = 1.77, 95% confidence interval (CI) = 1.03-3.04; P = 0.04] and the I/I genotype of the ACE I/D polymorphism (OR = 2.44, 95%CI = 1.78-3.35; P < 0.01) were identified. Statistically significant associations were also found for the PS1 1/2 polymorphism in both the dominant and recessive genetic models, whereas no association was found for the LRP C/T polymorphism. All studies exhibited heterogeneity (P < 0.05). This meta-analysis suggests that the 1/1 genotype of the PS1 1/2 polymorphism and the I/I genotype of the ACE I/D polymorphism are significantly associated with an increased risk of AD in the Chinese population.

Key words: Angiotensin-converting enzyme gene; Alzheimer's disease; Low-density lipoprotein receptor-related protein gene; Meta-analysis; Presenilin 1 gene; Polymorphism

INTRODUCTION

Alzheimer's disease (AD) is a common cause of morbidity and mortality among the elderly. The brains of patients with AD are essentially characterized by neuronal and synaptic loss, extracellular plaques composed of amyloid-β peptides, and intraneuronal neurofibrillary tangles consisting of hyperphosphorylated tau proteins. Genetic factors are believed to substantially contribute to an individual's risk of developing AD, but the apolipoprotein E4 (APOE4) allele is the only genetic factor unequivocally associated with an increased risk of late-onset AD (LOAD) (Sorbi et al., 1997; Bi et al., 2000), and it has been estimated to account for less than half of all AD genetic risk factors.

Wragg et al. (1996) were the first to allude to an association of variations in the biallelic polymorphism of the presenilin 1 (PS1) gene with risk of AD. Subsequent research efforts on PS1 have yielded inconsistent results, with some studies (Wu et al., 2002; Pritchard et al., 2005) showing an association between PS1 allele 1 and AD risk, while others (Hu et al., 2000; McIlroy et al., 2001; Bian et al., 2005) demonstrating the opposite.

Kehoe et al. (1999) were among the first to indicate an association between AD and the insertion/deletion (I/D) polymorphism in intron 16 of the angiotensin I-converting enzyme (ACE) gene. This potential association has since been examined in more than 40 studies worldwide, with mixed results (Chen et al., 2004).

Low-density lipoprotein receptor-related protein (LRP) is a cell receptor for APOE and is involved in mediating APOE-dependent neurite growth and in the neuronal metabolism of secreted β-amyloid precursor proteins (Kounnas et al., 1995; Sánchez-Guerra et al., 2001). Kang et al. (1997) were the first to report that a polymorphism in exon 3 of LRP is a risk factor for AD. Likewise, subsequent studies on this LRP polymorphism have produced inconsistent results, with some studies finding positive associations with the C allele (Kang et al., 1997; Wu, 2002) and others showing no association with AD (Wu et al., 1999; Zheng et al., 2004).

In China, genetic association studies are widely performed to evaluate the relationships between PS1, ACE, and LRP polymorphisms and AD risk. As with global population data sets, the obtained results for the Chinese population have been fairly inconsistent. In the present study, a meta-analysis of case-control studies assessing the associations between PS1

1/2, ACE I/D, and LRP C/T polymorphisms, and the risk of AD in the Chinese population was performed to clarify the issues inherent in this subject matter.

MATERIAL AND METHODS

Selection of studies

A systematic computerized literature search of studies published before August 12, 2010 was conducted using the Chinese Biomedicine Database, China National Knowledge Infrastructure, PubMed, and Medline. "Alzheimer's disease", "PS1", "ACE", "LRP", "polymorphism", "China", and "Chinese" served as the search terms.

Selection criteria

Studies were considered eligible for this meta-analysis if they met the following criteria: 1) patients with AD fulfilled the *DSM-III-R*, *DSM-IV*, and *NINCDS/ADRDA* criteria; 2) overall risk estimates were available; and 3) distributions of genotypes followed the Hardy-Weinberg equilibrium (HWE).

Data collection

Two separate reviewers examined the retrieved data and extracted the following information: author, year of publication, sample size, distribution of genotypes and alleles in both AD and control groups, and characteristics of the study participants.

Statistical analysis

The strengths of the associations between the three gene polymorphisms and AD were evaluated using odds ratios (ORs) and the corresponding 95% confidence intervals (CIs). Summary ORs based on the individual ORs were estimated using a random-effect model where there was heterogeneity between the studies; otherwise, a fixed-effect model was used. Statistical significance was determined using a *Z*-test. Funnel plots were used to investigate potential publication bias. All analytical procedures were performed using the Cochrane Review Manager (RevMan, version 5.0).

RESULTS

In total, 24 studies (12 for the PS1 gene, seven for the ACE gene, and five for the LRP gene), comprising 2611 patients with AD and 2822 control subjects from nine provinces and special districts in China, were included in this study.

The literature search identified 15 articles on the PS1 1/2 polymorphism, of which two duplicate publications and one review were excluded, leaving 12 articles for analysis (Table 1). The results of the meta-analysis on studies of the PS1 1/2 polymorphism are shown in Table 2.

According to the random-effect model, the summary ORs for 11/22, 12/22, 1/2, the dominant model, and the recessive model were 1.77 (95%CI = 1.03-3.04; P = 0.04), 1.45

(95%CI = 0.97-2.17; P = 0.07), 1.26 (95%CI = 0.99-1.61; P = 0.06), 1.68 (95%CI = 1.08-2.61; P = 0.02), and 0.68 (95%CI = 0.58-0.79; P < 0.01), respectively.

Table 1. Characteristics of studies included in the analyses and distribution of PS1 genotypes and alleles for cases and controls.

Source	Area	Sample age and gender				Genotype frequency [N (%)]			Frequency of 1 allele (%)
		Group	Sample size	Age	Gender (M/F)	1/1	1/2	2/2	
Tang et al. (1999)	Shanghai	AD	123	75.9 ± 8.9	59/64	49 (39.9)	59 (47.9)	15 (12.2)	36.2
		Control	140	71.6 ± 18.5	60/80	40 (28.6)	70 (50.0)	30 (21.4)	46.4
Ma et al. (2000b)	Guangdong	AD	75	81 ± 8	29/46	28 (37.3)	40 (53.3)	7 (9.3)	64.0
		Control	73	78 ± 8	39/34	17 (23.3)	38 (52.1)	18 (24.6)	49.3
Chen et al. (2004)	Guangdong	AD	66	67.9 ± 6.4	29/37	25 (37.9)	35 (53.0)	6 (9.1)	64.4
		Control	143	68.3 ± 6.0	65/78	33 (23.1)	75 (52.4)	35 (24.4)	49.3
Wu (2002)	Beijing	AD	135	73.63 ± 8.62	89/46	54 (40.0)	57 (42.2)	24 (17.8)	61.1
		Control	138	69.64 ± 5.43	57/81	63 (45.7)	65 (47.1)	10 (7.2)	69.2
Wu et al. (1998)	Shanghai	AD	71	76.9 ± 8.8		26 (36.6)	37 (52.1)	8 (11.3)	63.3
		Control	69	68.9 ± 6.0		31 (44.9)	28 (40.6)	10 (14.5)	65.2
Zhu et al. (2000)	Shandong	AD	32	73.1 ± 6.5		11 (34.4)	17 (53.1)	4 (12.5)	39.1
		Control	32	72.8 ± 6.85		12 (37.5)	18 (56.3)	2 (6.3)	34.3
Ma et al. (2000a)	Guangdong	AD	103	83 ± 12.6	41/62	38 (36.9)	47 (45.6)	18 (17.5)	59.7
		Control	98	80.6 ± 9.5	50/48	19 (19.4)	57 (58.2)	22 (22.4)	48.5
Bi et al. (1999)	Shandong	AD	43	73.2 ± 6.8		18 (41.9)	22 (51.2)	3 (6.9)	65.1
		Control	46	73.4 ± 7.5		23 (50.0)	20 (43.5)	3 (6.5)	68.5
Zhang et al. (2004)	Jiangsu	AD	144	71.5 ± 7.3	72/72	50 (34.7)	77 (53.5)	17 (11.8)	61.5
		Control	140	71.3 ± 7.6	71/69	25 (17.9)	74 (52.9)	31 (22.1)	51.4
Wu et al. (1999)	Shanghai	AD	91			39 (42.9)	44 (48.4)	8 (8.8)	67.0
		Control	73			29 (39.7)	34 (46.6)	10 (13.7)	63.0
Jia et al. (2006)	Hebei	AD	467	75.3 ± 7.3		196 (42.0)	239 (51.2)	32 (6.8)	67.6
		Control	480			124 (25.8)	254 (52.9)	102 (21.3)	52.4
Hu et al. (1998)	Taiwan	AD	55	78.2 (62-69)		23 (41.8)	25 (45.5)	7 (12.7)	64.5
		Control	93	79.2 (67-87)		42 (45.2)	41 (44.1)	10 (10.7)	67.2

Table 2. Meta-analysis of association between PS1 polymorphism and AD risk.

Gene polymorphism	I^2 (%)	Model	Pooled OR	OR (95%CI)	*Z*	P
1/2	75	Random effects	1.26	0.99-1.61	1.86	0.06
11/22	76	Random effects	1.77	1.03-3.04	2.05	0.04
12/22	60	Random effects	1.45	0.97-2.17	1.83	0.07
Recessive	61	Random effects	0.68	0.58-0.79	5.00	<0.01
Dominant	70	Random effects	1.68	1.08-2.61	2.31	0.02

For the LRP C/T polymorphism, the literature search identified 12 articles, of which five met the selection criteria (Table 3). Among the seven excluded articles, two were duplicated publications, three did not follow the HWE model, and two did not report the distribution of genotypes. The results of the meta-analysis are shown in Table 4.

According to the random-effect model, the summary ORs for T/C, CT/CC, and the dominant model were 0.80 (95%CI = 0.45-1.44; P = 0.46), 0.80 (95%CI = 0.43-1.47; P = 0.47), and 0.81 (95%CI = 0.49-1.37; P = 0.44), respectively. In the fixed-effect model, the summary ORs for TT/CC and the recessive model were 0.59 (95%CI = 0.19-1.85; P = 0.37) and 1.47 (95%CI = 0.47-4.58; P = 0.51), respectively.

Thirteen articles were identified for the ACE I/D polymorphism, of which seven met the selection criteria (Table 5). Among the six excluded articles, three were duplicated publications and three did not follow the HWE model. The results of the meta-analysis are shown in Table 6.

Table 3. Characteristics of studies included in the analyses and distribution of LRP genotypes and alleles for cases and controls.

Study	Area	Sample age and gender				Genotype frequency [N (%)]			Frequency of C allele (%)
		Group	Sample size	Age	Gender (M/F)	C/C	C/T	T/T	
Chen et al. (2009)	Shanxi	AD	67	71.93 ± 7.23	44/23	59 (88.1)	8 (11.9)	0 (0.0)	94.0
		Control	77	70.04 ± 4.31	42/35	56 (72.7)	19 (24.7)	2 (2.60)	85.1
Bi et al. (2000)	Heilongjiang	AD	42	60-79	23/19	33 (78.6)	7 (16.7)	2 (4.7)	86.9
		Control	40	60-81	24/16	23 (57.5)	13 (32.5)	4 (10.0)	73.8
Zheng et al. (2004)	Guangxi	AD	79	72.8 ± 9.5	40/39	72 (91.1)	6 (7.6)	1 (1.3)	94.9
		Control	156	71.2 ± 9.3	92/64	139 (89.1)	16 (10.3)	1 (0.6)	94.2
Hu et al. (2000)	Taiwan	AD	82	78.2 (62-69)		66 (80.5)	16 (19.5)	0 (0.0)	90.2
		Control	110	79.2 (67-87)		98 (89.1)	12 (10.9)	0 (0.0)	94.5
Bian et al. (2005)	Shanghai	AD	216			189 (87.5)	26 (12.0)	1 (0.5)	93.5
		Control	200			179 (89.5)	21 (10.5)	0 (0.0)	94.8

Table 4. Meta-analysis of association between the LRP gene polymorphism and AD risk.

Gene polymorphism	I^2 (%)	Model	Pooled OR	OR (95%CI)	*Z*	P
T/C	66	Random effects	0.80	0.45-1.44	0.74	0.46
TT/CC	0	Fixed effects	0.59	0.19-1.85	0.90	0.37
CT/CC	62	Random effects	0.80	0.43-1.47	0.73	0.47
Dominant	58	Random effects	0.81	0.49-1.37	0.78	0.44
Recessive	0	Fixed effects	1.47	0.47-4.58	0.66	0.51

Table 5. Characteristics of studies included in the analyses and distribution of ACE genotypes and alleles for cases and controls.

Study	Area	Sample age and gender				Genotype frequency [N (%)]			Frequency of D allele (%)
		Group	Sample size	Age	Gender (M/F)	D/D	I/D	I/I	
Liu et al. (2007)	Jiangsu	AD	39	70.2 ± 7.8	15/24	5 (12.8)	12 (30.8)	22 (56.4)	28.2
		Control	50	72.1 ± 7.3	26/24	11 (22.0)	21 (42.0)	18 (36.0)	43.0
Wu et al. (2002)	Beijing	AD	96	71.5 ± 6.1	33/63	12 (12.5)	44 (45.8)	40 (41.7)	35.4
		Control	96	70.1 ± 5.4	33/63	25 (26.0)	47 (49.0)	24 (25.0)	50.5
Han and Zhang (2008)	Shanxi	AD	55	75.5 ± 9.3	34/21	12 (21.8)	19 (34.6)	24 (43.6)	39.1
		Control	59	72.3 ± 8.0	35/24	10 (17.0)	32 (54.2)	17 (28.8)	44.1
Wang et al. (2006)	Taiwan	AD	151	74.8 ± 7.9	62/89	27 (17.9)	59 (39.1)	65 (43.0)	37.4
		Control	161	62.5 ± 8.7	85/76	9 (5.6)	59 (36.6)	93 (57.8)	34.7
Ning et al. (2010)	Shanghai	AD	138			17 (12.3)	39 (28.3)	82 (59.4)	26.4
		Control	469			67 (14.3)	229 (48.8)	173 (36.9)	36.9
Li (2003)	Guangxi	AD	68		26/42	7 (10.3)	21 (30.9)	40 (58.8)	25.7
		Control	156		105/52	19 (12.1)	77 (49.4)	60 (38.5)	36.9
Cheng et al. (2002)	Taiwan	AD	173	74.4 ± 6.4	97/76	9 (5.2)	79 (45.7)	85 (49.1)	28.0
		Control	286		145/141	39 (13.6)	126 (44.1)	121 (42.3)	37.7

Table 6. Meta-analysis of association between the ACE I/D polymorphism and AD risk.

Gene polymorphism	I^2 (%)	Model	Pooled OR	OR (95%CI)	*Z*	P
I/D	89	Random effects	1.41	0.88-2.26	1.42	0.16
II/DD	0	Fixed effects	2.44	1.78-3.35	5.54	<0.01
ID/DD	69	Random effects	0.95	0.70-1.28	0.35	0.72
Dominant	71.59	Random effects	0.62	0.31-1.22	1.38	0.17
Recessive	78	Random effects	1.28	0.66-2.50	0.73	0.46

The summary OR for II/DD was 2.44 (95%CI = 1.78-3.35; P < 0.01) in the fixed-effect model. According to the random-effect model, the summary ORs for ID/DD, I/D, the dominant model, and the recessive model were 0.95 (95%CI = 0.70-1.28; P = 0.72), 1.41 (95%CI = 0.88-2.26; P = 0.16), 0.62 (95%CI = 0.31-1.22; P = 0.17), and 1.28 (95%CI = 0.66-2.50; P = 0.46), respectively.

DISCUSSION

The present study differs from previous meta-analyses in that it focused on the Chinese population. The most extensive studies on the three polymorphisms, including recently published articles and all related articles published in English and Chinese, were included.

One meta-analysis disclosed a significant association between the PS1 1/1 genotype and LOAD in both Caucasian and Japanese populations (Pritchard et al., 2005). Another meta-analysis found that the PS1 2/2 genotype is a risk factor for LOAD in the Spanish population (Chen et al., 2009). Owing to language restrictions, only two studies in the Chinese population were included in that meta-analysis. Hence, the specific objective of the present meta-analysis was to examine whether PS1 is associated with AD in the Chinese population.

The positive association of the PS1 polymorphism with AD may be attributed to the polymorphism itself as well as the disequilibrium between this locus and another active locus in the PS1 gene. This study attempted to further investigate possible interactions between the APOE and PS1 genes, but the limited number of eligible studies made this impractical.

LRP is known to facilitate the delivery of cell surface amyloid precursor proteins to indusial compartments. Sánchez-Guerra et al. (2001) conducted a meta-analysis of eight studies and found a weak correlation between the LRP CC genotype and AD. Pritchard et al. (2005) performed a meta-analysis on the data of 4668 patients with AD and 4473 control subjects but found no evidence for the involvement of the LRP C/T polymorphism in either increasing the susceptibility to AD, or acting as a phenotypic modifier. However, only two studies on the Chinese population were included in their meta-analysis. To examine whether the LRP C/T polymorphism is associated with AD in the Chinese population, the present study included five studies involving 484 patients and 583 control subjects; however, no association between the LRP C/T polymorphism and AD risk was observed. Previous research on the relationship between LRP gene polymorphisms and AD risk has used a smaller number of publications and samples, and the positive findings might have been obtained by chance.

The association between the ACE I/D polymorphism and AD was similar across different ethnic groups. Elkins et al. (2004) found that the I allele of the ACE I/D polymorphism is associated with an increased risk of LOAD. In addition, their studies involving Asian subjects demonstrated a more robust and consistent association between the I allele and AD than those involving Caucasian subjects. In another meta-analysis (Chen et al., 2004), three ethnic groups (North European, South Caucasian, and East Asian subjects) were examined, and the results confirmed the association between ACE I/D and AD across diverse populations. Both meta-analyses suggested that the I allele increased the risk of AD. Only two studies conducted on the Chinese population were available, one of which did not follow the HWE model (Sánchez-Guerra et al., 2001), and, therefore, no conclusions could be drawn for the association between ACE polymorphisms and AD risk.

The association between ACE polymorphisms and AD suggests that the ACE I/D polymorphism is closely linked to the disequilibrium of another truly causal polymorphism

in ACE. Indeed, rs4291 and rs4343 have been reported to be linked to the disequilibrium in the I/D polymorphism (Saunders et al., 1993); moreover, rs4291 polymorphisms have shown significant summary ORs in the AlzGene (Bertram and Tanzi, 2004). Previous research has also confirmed that the rs4343 A allele is associated with the risk of LOAD in the Chinese population (Hollenbach et al., 1998).

Several limitations should be considered in interpreting our results. First, owing to data limitations, the studies could not be divided into subgroups by age. Second, owing to the lack of original data, an evaluation of potential interactions (e.g., gene-gene and genetic-environment) was not performed, which may have influenced the results. Third, publication bias might have occurred when the effect of PS1 1/2 on AD risk was investigated. This study did not investigate any possible publication bias for the data on LRP and ACE, as fewer than nine articles were identified. Furthermore, with only published studies considered for the meta-analysis, publication bias might have affected the findings.

CONCLUSIONS

The PS1 1/2 genotype and the ACE I/D genotype are significantly associated with an increased risk of AD in the Chinese population. Further large-scale studies are necessary to confirm our findings and inform a better understanding of the associations between PS1 1/2, ACE I/D, and LRP C/T polymorphisms, and AD.

Conflicts of interest

The authors declare no conflict of interest.

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